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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,600	03/24/2006	James Wilson	UPN-P3230USA	6834

270 7590 01/22/2010

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
01/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/573,600	WILSON ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,43,45 and 59-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,43,45 and 59-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/9/09 has been entered. Claims 32, 43, 45 and 59-69 are pending.

Information Disclosure Statement

An information disclosure statement filed 11/9/2009 has been identified and the documents considered. The corresponding signed and initialed PTO Form 1449 has been mailed with this action. The documents listed as Search Reports and office *have been considered* but has been crossed off the 1449 so that it will not appear on the face of any patent issuing from the instant application. These submissions do not constitute documents under 37 CFR 1.98.

Claim Objections

Claims 45, 59, 62-64 and 67 are objected to because of the following informalities: claim 45 recites "a non-naturally occurring AAV according to claim 59". However, when referring to previous limitations, it is proper to use the article --the-- as opposed to "a" which implies a new limitation. As well, in claim 45, the phrase "said

rAAV" is incorrect. When using the phrase "said" the limitation is repeated as previously recited in exact terms. In this case, the term rAAV does not appear in the claims.

Claim 59 is awkward in the recitation "the amino acid sequence of SEQ ID NO:123 over amino acids 1 to 736". It would be more direct to recite --amino acids 1-736 of SEQ ID NO:123--. Similar amendment to claim 65 is recommended.

Claim 62 requires amendment of "a non-naturally occurring AAV" to --the--. Similar amendment to claim 63 is required.

In claim 64 an article is required prior to each of low density, high density . As well, the transgene is not selected from the group but --the transgene encodes a protein selected from the group--.

Claim 67 separates members of the group using semicolons whereas it would be proper to use commas.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59, 65 and 67-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements.

See MPEP § 2172.01. The omitted elements are: what makes the AAV non-naturally occurring. The claim solely encompasses elements that are or could b e part of naturally occurring AAV i.e. SEQ ID NO:123. It appears from the specification (see 112, first rejection below) as if the AAV is non-naturally occurring due to the inclusion of heterologous gene sequences.

Claim 65 recites the limitation "the heterologous gene" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claims 67 -69 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what makes the AAV non-naturally occurring. The claim recites specific sequence by numbers but do not list the source of the sequences. Absent the source sequence, it is not clear to what the numbers correlate.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated recombinant AAV comprising an AAV9 capsid wherein the AAV9 capsid is SEQ ID NO:123 or comprises amino acids 203-736 of SEQ ID NO:123 or an isolated chimeric capsid vp1, vp2 or vp3 protein wherein the chimeric

capsid protein comprises sequences from SEQ ID NO:123 selected from the group consisting of aa25-28, aa137-143, aa154-156, aa171-173, aa182-186, aa185-198, aa260-273, aa262-264, aa261-274, aa262-274, aa381-383, and aa670-706, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a 1) a non-naturally occurring AAV comprising an AAV9 capsid with at least 95% identity to SEQ ID NO:123, compositions comprising and methods of administering 2) an AAV9 capsid comprising an AAV9 capsid selected form vp1, vp2 and vp3, compositions comprising and methods of administering, 3) an AAV comprising an AAV9 capsid comprising at least 95% identity to amino acids 203-736 of SEQ IDNO:123 or 90% identity to amino acids 1-706 of SEQ IDNO:123 and 4) capsid proteins comprising an AAV9/HU.14 capsid protein fragment as recited in claim 67 fused to one or more heterologous capsid protein fragments. By recitation of the protein in terms of identity and proteins comprising an AAV 9 fragment fused to one or more heterologous capsid proteins, a potentially large number of proteins are actually

recited of which most that may or may not encode a protein with the capabilities of capsid function. Regarding item 1 and 3, the specification teaches only SEQ ID NO:123 and does not provide those variable amino acids nor any fragments such that a person of skill in the art would recognize those amino acids that are related by 95% or 90% with capsid function. Regarding item 2, the claim is drawn to a capsid comprising a single protein whereas the specification and art as regards AAV9 has demonstrated that a capsid requires vp1, vp2 and vp3 to form a capsid. As to item 4) the recitation that the capsid protein only requires "one or more AAV capsid protein fragments from one or more different AAVS" encompasses a number of non-productive fragments that even in combination with the recited AAV9 fragments will not form a capsid protein. The breadth of enabled subject matter is not commensurate in scope with the claims. The amount of direction presented and the number of working examples provided in the specification are very narrow compared to the breadth of claims at issue. MPEP 2164.05 teaches, "However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." In this case, the specification teaches only that SEQ ID NO:123 is essential to form a capsid or else use of a number of sequences in the context of an entire capsid protein. However, the claims are directed to a large genus of proteins that are variants and fragments with no requirement of structure.

As to nucleic acids and proteins that are 95% or 90% identical to SEQ ID NO:123, the following considerations must be made. The specification discloses that SEQ ID NO:123 is 736 amino acids. And while the disclosure states that any peptide with at least 95% or at least 90% identity can be used in the AAV, the disclosure does not demonstrate what sequences must be retained and what sequences are dispensable. For proteins with 10% variability of sequence, a protein of 736 amino acids can have as many as 74 different *combinations* of amino acids mutated. 74 mutational combinations, randomly made, amounts to characterizing the structure for allowable mutations. For nucleic acids, 5% variability means that 36 amino acids can be altered. For fragments, in the face of missing structural requirements, there exist a large genus of sequences comprising any number of non-functionally as well as functionally active fragments that do not affect the instant invention. However, the ability to determine *a priori* whether a variant or unknown sequence will encode a protein with a particular activity is not a high art. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness (see Guo et al and Lesk et al). Here, the question is can the functionality of variants and fragments be known with predictability. Lesk teaches the lack of predictability of claiming variants of a protein even with a known function.

> *Nevertheless, prediction of protein function from sequence and structure is a difficult problem, because homologous proteins often have different functions. Many*

> *methods of function prediction rely on identifying similarity in sequence and / or structure between a protein of unknown function and one or more well-understood proteins*. Alternative methods include conservation patterns in members of a functionally uncharacterised family for which many sequences and structures are known. However, these inferences are tenuous. Such methods provide reasonable guesses at function, but are far from foolproof

As demonstrated by Lesk, methods of function prediction rely on comparison of proteins of known function with those of unknown function. In this case, the protein (SEQ ID NO:6) is used to derive function from a randomly modified protein, however, prediction of function from sequence is difficult because even homologous proteins have different function. Lesk clearly confirms that predictability of ascribing the same function as SEQ ID NO:6 to protein variants is unpredictable.

> In most cases, predictions suggest, but do not determine, the general class of function. Their most useful effect is to guide investigations in the laboratory to confirm, or refute, the prediction, and, even if correct, to define the function in greater detail.
> We conclude that predictions are useful but no substitute for work in the laboratory. Indications from theory may indict, but only experimental evidence can convict.

Guo et al teach that the probability that a protein will tolerate a substitution or random alteration requires a clear understanding of the structural-functional correlations of the protein.

> However, to date, we lack a quantitative measure of the degree of proteins' tolerance for random amino acid changes that occur at a random position in the protein. If a rigorous measure of proteins' degree of tolerance of random amino acid changes can be defined, then such fundamental calculations as the steepness of protein fitness landscapes or the rate of introduction of deleterious mutations into coding genomes can be more clearly delineated. Further understanding of the nature of tolerated amino acid substitution's can also lend !insight into protein folding, and design

Guo et al suggest that an understanding as to the critical region and defining the "x-factor" allow one to predict the probability that a change will be inactivating or will be tolerated are required. However, the instant case, does not propose substitutions of

specific regions. Rather, the invention relies on random mutagenesis with the assumption that so long as 90% of the protein is the same then the resulting function will be the same.

Furthermore, Richards (1997) *Cell Mol. Life Sci.* 53:790-802 teaches, "In terms of structural alterations and thermostability, responses to genetic mutations are context dependent and remain difficult to predict with any confidence." (Abstract, column 1.) Thus, Richards teaches that the effect of mutation on protein stability, a prerequisite for biological function, is unpredictable. Richards also teaches that even limited amino acid modifications can have dramatic effects on protein structure and function. In the second column on page 791, Richards cites the example of influenza virus hemagglutinin protein, wherein alterations in the ionization state of just a few ionizable groups dramatically alters the biological behavior of the molecule. Citing a published study of done on the gene V protein, Richards teaches that, in spite of only limited modification at two amino acid positions, "The effects on the overall stability of the protein were remarkably variable." (page 794, column 1). In the paragraph bridging pages 796 and 797, Richards teaches, "In single site mutants, the structural changes are generally greatest near the site of mutation, and moving away, decrease radially in all directions. *Even the small changes are so complex that the linkage relations do not allow assignments of the energetic changes to unique parts of the altered residue and its immediate contacts*" (emphasis added) and "There is no convincing explanation yet of how the changes in binding can produce a major movement over such a distance." Finally, in the first full paragraph in the second column on page 793, Richards teaches, "Almost all mutations are accompanied by some conformational change, making prediction of the effects on stability difficult. *In most cases mutations lead to lowering of*

the stability." (Emphasis added.) Thus, Richards teaches that small changes in the primary structure of a protein frequently have dramatic effects on the higher order structure and function of the protein, and that these effects are highly unpredictable. However, applicants propose mutation of 74 and 37 amino acids which according to the art can alter function and 3d integrity even at the level of a single amino acid mutation.

Regarding the recitation in claim 60 and 61 of capsids only requiring one of vp1, vp2 and vp3,

> [0091] Particularly desirable proteins include the AAV capsid proteins. which are encoded by the nucleotide sequences identified above. The AAV capsid is composed of three proteins, vp1, vp2 and vp3, which are alternative splice variants. The full-length sequence provided in FIG. 2 is that of vp1. The AAV9/HU.14 capsid proteins include vp1 [amino acids (aa) 1 to 736 of SEQ ID NO: 123], vp2 [about aa 138 to 736 of SEQ ID NO: 123], vp3 [about aa 203 to 736 of SEQ ID NO: 123], and functional fragments thereof. Other desirable fragments of the capsid protein include the constant and variable regions, located between hypervariable regions (HVR). Other desirable fragments of the capsid protein include the HVR themselves.

The specification does not teach that a capsid comprised of a single protein is possible. It appears as if a chimeric capsid can be created wherein one of the proteins is from AAV9. However, at the time of filing, it isn't clear that an AAV9 vp1, vp2 or vp3 protein alone would suffice to create this capsid. As well, claims 67-69 recite a capsid "protein" which must comprise one of aa25-28, aa137-143, aa154-156, aa171-173, aa182-186, aa185-198, aa260-273, aa262-264, aa261-274, aa262-274, aa381-383, and aa670-706 and a fragment of at least on other AAV serotype capsid. This encompasses a number of combinations which are not structurally or functionally limited. In other words, there is

no indication if these fragments can substitute a full length similar region fragments what this region would be or if any additional fragment will suffice to create a capsid protein.

Given the large size and diversity of the recited sequences, the absence of disclosed or art recognized correlations between structure and function and the large number of potential sequences or homologues, variants, and fragments and in view of the unpredictability of the art of predicting the functional and structural nature of homologues, variants, and fragments of SEQ ID NO:123: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/ functional characteristics of a protein from primary sequence alone, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Furthermore, the relationship of enablement with the requirement for written description is acknowledged by the MPEP. To this end, the court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the molecule itself. It is not sufficient to define a protein solely by its

principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any protein with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a amino acids, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all peptides that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all protein with a specific function and the specification discloses but a single one known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 ' of§112. Specifically, in the instant case, applicants propose a functional relationship of the related and fragmentary amino acids, but there is no requirement either in the claims or the specification for structural requirements such that the structure-function relationship can be determined or so that the genus of peptides claimed is commensurate in scope with the disclosure.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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